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Recurrence and Progression in Meningiomas: The Clonal Cytogenetic Evolution of a Benign Human Tumour

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Abstract: Meningiomas are mostly benign tumours that originate from the coverings of brain and spinal cord. Only a minority of cases show progression to an anaplastic tumour (WHO grades II and III). Multiple and familial cases are rare and mostly associated with (hereditary) neurofibromatosis 2 (NF2). Meningiomas show an unexpectedly high recurrence rate. Also, completely removed low-grade tumours can recur. On a cytogenetic level, meningiomas are the best-studied tumours in humans. The majority of high-grade but only a minority of low-grade meningiomas show loss of merlin, a cytoskeleton-cytoplasm-linker protein. Merlin is the product of the NF2 gene located on chromosome 22. A second tumour suppressor gene on chromosome 22 on 22q12.3 is the gene for the tissue inhibitor of metalloproteinase 3 (TIMP3), which appears to be involved in meningioma pro-

gression and a high-grade meningioma phenotype. In contrast to other solid tumours, progression of meningiomas is correlated with increasing hypodiploidy, showing characteristic clonal evolutions that mostly include chromosomes 14, 18, and 19 and, more rarely, 6 and 10. Structural aberrations are rare, except for the loss of the short arm of one chromosome 1, which appears to be the decisive step for anaplastic growth. A biostatistical approach has been proposed, using an oncogenetic tree model that estimates the most likely cytogenetic pathways of meningioma patients in terms of accumulation of chromosome changes in tumour cells. The genetic progression score (GPS) estimates the genetic status of a tumour as progression in the corresponding tumour cells along this model. High GPS values are highly correlated with early recurrence of meningiomas

($p < 10^{-4}$). This correlation holds true even when patients are stratified by WHO grade. Tumour location also has an impact on genetic progression. Clinical relevance of the GPS is demonstrated with respect to origin, WHO grade, and recurrence of the tumour. As a quantitative measure, the GPS allows a more precise assessment of the prognosis of meningiomas than categorical cytogenetic markers based on single chromosomal aberrations. Comparative histochemical and molecular cytogenetic studies point to the alkaline phosphatase gene (ALPL, liver-bone-kidney type) located on 1p36.1–p34 as a candidate tumour suppressor gene. **Eur Assoc NeuroOncol Mag 2013; 3 (3): 105–11.**

Key words: meningioma, recurrence, deletion of 1p, chromosomes, genetic progression

■ Introduction

Meningiomas are derived from the arachnoidal cap cells of the leptomeninges, the soft coverings of the brain and spinal cord. Although their matrix tissue constitutes < 5 % of the intracranial and intraspinal masses, meningiomas are estimated to constitute between 13 % and 26 % of the primary tumours within the CNS. Most meningiomas are sporadic, slowly growing benign tumours and correspond histologically to WHO grade I. However, certain histological subtypes and also a minority of common-type meningiomas show a more aggressive biological behaviour and are associated with an increased risk of recurrence and an unfavourable prognosis. Corresponding to their localization, meningiomas of the spinal cord tend to be significantly more benign than those of the brain basis, which, in turn, are more benign than meningiomas of the brain convexity [1, 2]. The current WHO classification of brain tumours [1] distinguishes 3 grades of meningiomas: the common type (WHO grade I), the atypical or intermediate type (WHO grade II), and the anaplastic (WHO grade III) meningioma.

For appropriate treatment of tumour patients, prediction of time until death or time to progression after initial treatment is an important task. Due to many clinical, topographical, radiological, and surgical factors, histology is not solely decisive for prognosis [3], although mitotic activity, cellular pleomorphism

with prominent nucleoli and micronecrosis, and focally raised cell density have been discussed as indicators of a poorer prognosis [4]. A major challenge is the identification of genetic prognostic markers that better reflect tumour biology.

Multiple occurrences are rare events, observed in only about 2 % of cases. Frequently, multiple meningiomas occur in patients with neurofibromatosis 2 (NF2), an autosomally dominant tumour syndrome, in combination with vestibular schwannomas and ependymomas. A polyclonal origin must be supposed in these cases.

In non-NF2 cases, molecular genetic studies demonstrate a common clonal origin of multiple or recurrent meningiomas [5, 6]. The development of familial (multiple) meningiomas within the same or different generations has so far been reported in < 20 families. Pathologic and genetic data on these families first suggested a biologically variant type of NF2 with the development of meningiomas only but no schwannomas. Molecular studies on a few cases indeed excluded the involvement of the NF2 gene although a chromosome 22 was missing. Alternatively, homozygous inactivation of a different tumour suppressor gene on the same chromosome was proposed [7].

The meningioma is one of the cytogenetically best-studied solid tumours. The characteristic and most frequent chromosomal aberration in meningiomas is monosomy 22 [8], which, however, seems not to be relevant for prognosis as an isolated anomaly. The progression from common-type to atypical and anaplastic meningioma is characterized by 2 different cytogenetic events: Firstly, further loss of up to 6 other chromosomes, with a mostly typical pattern of clonal evolution, and, secondly, partial or complete loss of the short arm of one chromosome 1 [3, 9–15].

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The identification of pathogenetic pathways in human tumours is one of the main challenges in molecular oncology. For many tumour types, genetic events defined by somatic chromosome alterations or gene mutations, respectively, are known to accumulate over time in the course of the disease. Based on these findings, genetic changes associated with chromosome instability are believed to play an important role in both tumourigenesis and tumour progression in meningiomas. There is a vast amount of literature on linking single genetic alterations to survival [16], but only few efforts have been made to construct more complex and comprehensive markers. Zang [15] described a first model of clonal evolution in meningiomas based on conventional cytogenetic studies. Data of the cytogenetic findings of 394 meningiomas led to an empirical model of meningioma progression.

Cytogenetic analyses show that numerical and structural chromosome changes with pronounced hypodiploidy, or rarely hyperdiploidy [17], and especially deletion of the short arm of a chromosome 1, are accompanied by more aggressive biological characteristics [3, 9–15, 18].

By using a mathematical model for estimating the most likely cytogenetic pathways in meningiomas, a model for tumour recurrence could be established. In this model, each tumour is represented by the genetic events that have occurred in the tumour. The most important difference of the mathematical model compared to the “hand-crafted” model [15] is that it allows an objective assignment of the estimated time to recurrence for a single tumour based on its genetic status.

Incidence, Materials, and Statistics

Patient Population

We performed a retrospective study on 661 patients (482 women and 179 men) with meningiomas operated on at the Department of Neurosurgery, Saarland University, between January 1973 and April 2005. Average age of the overall patient population was 57.3 years ($SD \pm 12.8$ years). Average age of the female patients was 57.6 years ($SD \pm 12.3$ years), average age of the male patients was 56.7 years ($SD \pm 14.1$ years).

Clinical Variables

The clinical variables investigated comprise patient gender and age, tumour location and histology, and the completeness of tumour extirpation.

Location

We formed 9 groups depending on meningioma location: (1) convexity, (2) parasagittal region, (3) tuberculum sellae, (4) olfactory groove, (5) sphenoid wing ridge, (6) posterior cranial fossa, (7) tentorium, (8) ventricular, and (9) spinal channel. The classification was carried out on the basis of the preoperative CT and NMR.

Tumour Extirpation

Complete surgical extirpation of the tumour was defined as Simpson grades I and II corresponding to a macroscopically complete tumour resection with bipolar coagulation of the dura insertion.

Tumour Histology

The 661 cases investigated comprised 465 common-type (WHO grade I), 156 intermediate-type (WHO atypical meningioma, grade II), and 14 anaplastic meningiomas (WHO grade III). Meningioma grade was assessed by a combined histological and morphometric approach on routinely HE and Ki-67/Feulgen-stained, formalin-fixed, paraffin-embedded tissue sections [12].

Cell Culture and Cytogenetic Preparation

Cell cultures from 661 meningioma biopsies and chromosome preparations with GTC banding were carried out according to standard procedures. Many tumours were characterized by multiple patterns of cytogenetic aberrations. In total, 1068 clonal patterns were observed in the 661 tumours.

Histochemical Detection of ALPL

The histochemical findings shown in Figure 1 were performed on frozen sections as described by Niedermayer et al [3].

Follow-up

Patients were investigated in the neurosurgical outpatient department of the Saarland University, either within the framework of routine follow-up or because of the appearance of neurological symptoms. Recurrence was evaluated as new evidence of a tumour in CT or NMR after previous complete extirpation (Simpson grades I and II). The Simpson grade II was established on the basis of the operation report and the postoperative CT or NMR investigation. Average follow-up time was 40.3 months (41.5 months for female patients and 37.2 months for male patients).

Statistical Analyses

Oncogenetic Tree Models

Mixtures of oncogenetic trees were used to describe the ordered accumulation of genetic aberrations during tumour progression. In a single oncogenetic tree, vertices represent genetic events, and edges between vertices represent transitions between the events. Each edge is associated with the probability that the successor event will occur, given the predecessor event has already occurred. In the model, genetic events are assumed to be non-reversible, thus the disease process can be fully described by the accumulation of genetic aberrations. In the mixture model, more than one tree component is estimated [18].

Genetic Progression Score

In oncogenetic tree models, consecutive genetic aberrations are associated with corresponding conditional transition probabilities. These probabilities can be converted to average waiting times by assuming Poisson processes for the occurrence of aberrations (see Rahnenführer et al [19] for details). Formally, waiting time associated to an edge of the tree with corresponding conditional probability p is given by $(1-p)/p$ multiplied with a scaling factor that is typically set to 1. The genetic progression score (GPS) of a tumour then is defined as the average waiting time of its pattern of genetic aberrations, given the underlying tree mixture model. Tumours with few aberrations that appear early in the model receive low GPS values; tumours with many late aberrations in the model are associated with high GPS values. For 221 out of the 661 pa-

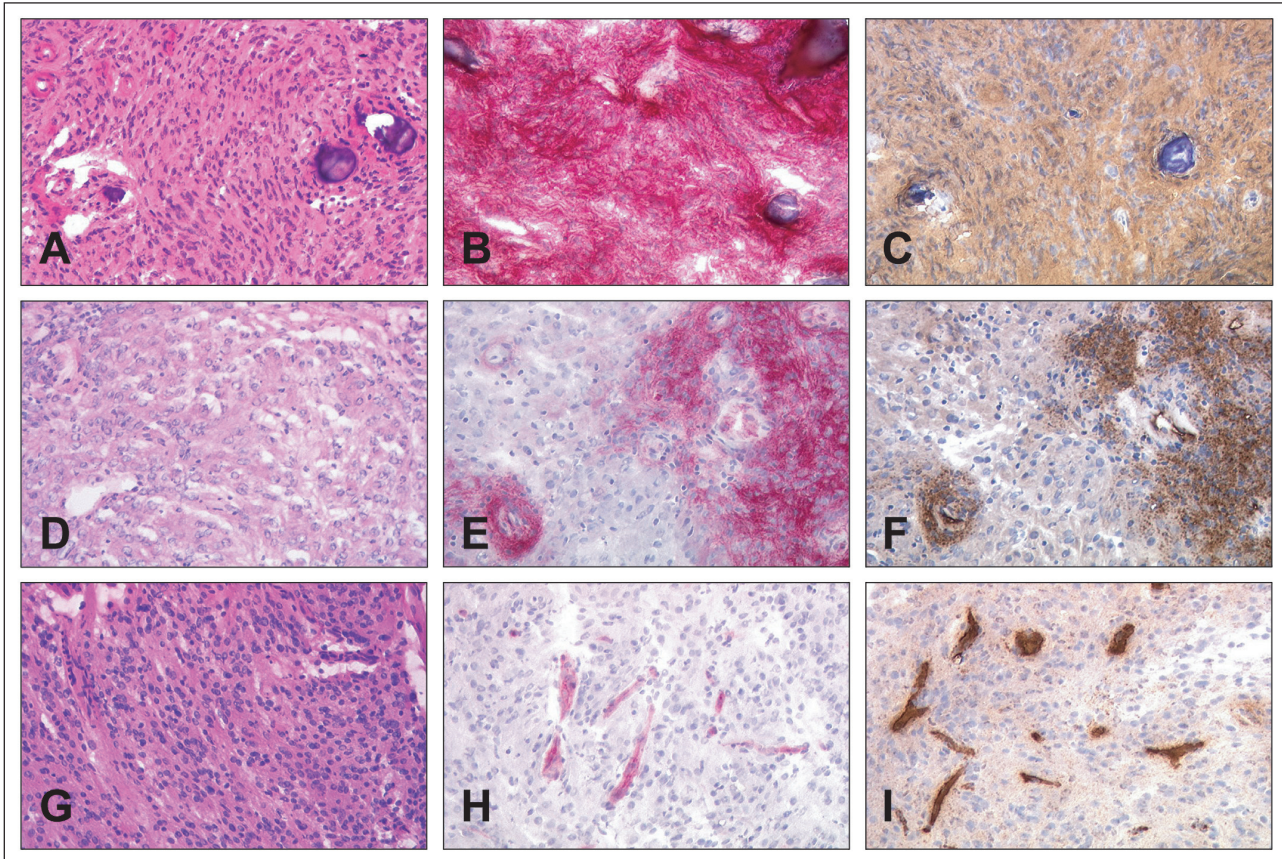


Figure 1. Expression pattern of alkaline phosphatase in meningiomas of different grade (liver-bone-kidney type, ALPL, located at 1p36.1–p34). In the rows, parallel sections of meningiomas are shown. The upper row (A–C) shows a WHO grade-I, the middle row (D–F) a grade-II, and the lower row (G–I) a grade-III meningioma.

The first column shows haematoxylin and eosin stainings, the second column histochemical alkaline phosphatase reactivity, and the third column immunohistochemical localization of the alkaline phosphatase protein. Histochemical and immunohistochemical stainings show a very good correlation. In the grade-I meningioma, all tumour cells are positive; in the grade-II tumour, clearly delineated areas are spared, and in the grade-III meningioma only the endothelial cells of the blood vessels are positive, the tumour cells being completely negative histochemically as well as immunohistochemically. Loss of ALPL expression is highly correlated with FISH results on the terminal 1p deletion. All sections were photographed with a 20× objective. Reprinted with permission from [Zang KD. Meningioma: a cytogenetic model of a complex benign human tumor, including data on 394 karyotyped cases. *Cytogenet Cell Genet* 2001; 93: 207–20.] © 2001 Karger Publishers, Basel, Switzerland.

tients, more than one cytogenetic pattern was detected. In these cases, the GPS of the tumour was defined as the highest GPS of all clones found in the tumour.

■ Clinical Factors of Meningioma Prognosis

Grading of meningiomas has always been controversial. Obviously, the biological behaviour of meningiomas cannot be accounted for by histological parameters alone [14, 15]. In 1979, Zülch stated that it is not the histological grading which is most crucial for the rate of recurrence of meningiomas, but primarily the completeness of extirpation [20]. There is agreement in the literature that radical surgical extirpation is correlated with a good prognosis [21, 22].

It is well known that females are affected far more frequently by meningiomas than males [20, 21]. This observation was confirmed in our previous study [12, 14, 15] with a ratio of 2.67:1. In particular, in the 49 spinal tumours investigated, the female sex was overrepresented (87 %). This sex ratio was shifted when the tumours were broken down by karyotype. In the GPS group 2 (GPS ≥ 6.39), ie, in tumours with a pronounced aberration of the karyotype with deletion 1p, we found a sex distribution of 1.81:1.

■ Cytogenetic Aspects of Meningiomas

Localization of Meningiomas

Frequency and behaviour of meningiomas at different intracranial locations were first discussed in 1922 [23]. A correlation between tumour localization and malignancy has repeatedly been observed. Meningiomas of the spinal cord tend to be significantly more often benign than those of the brain basis, which, in turn, are more often benign than meningiomas of the convexity [1, 2]. In 1980, it was shown that tumours located at the base of the skull typically contain cells with 46 chromosomes, whereas meningiomas located at the convexity show significant numbers of chromosomal aberrations [15]. In spinal tumours, almost exclusively a 22-monosomic karyotype was detected. It was already striking at that time that meningiomas which recurred showed significantly more chromosomal aberrations and a preference of the convexity. These findings are also in line with the results of a large series of meningioma patients ($n > 9000$ cases), where benign meningiomas were more frequently located at the skull than malignant meningiomas ($p < 0.02$) (Figure 2) [2].

Cytogenetic Findings and Histomorphology

Among histopathologically prognostic parameters, mitotic activity is the most important one. As the cut-offs of mitotic

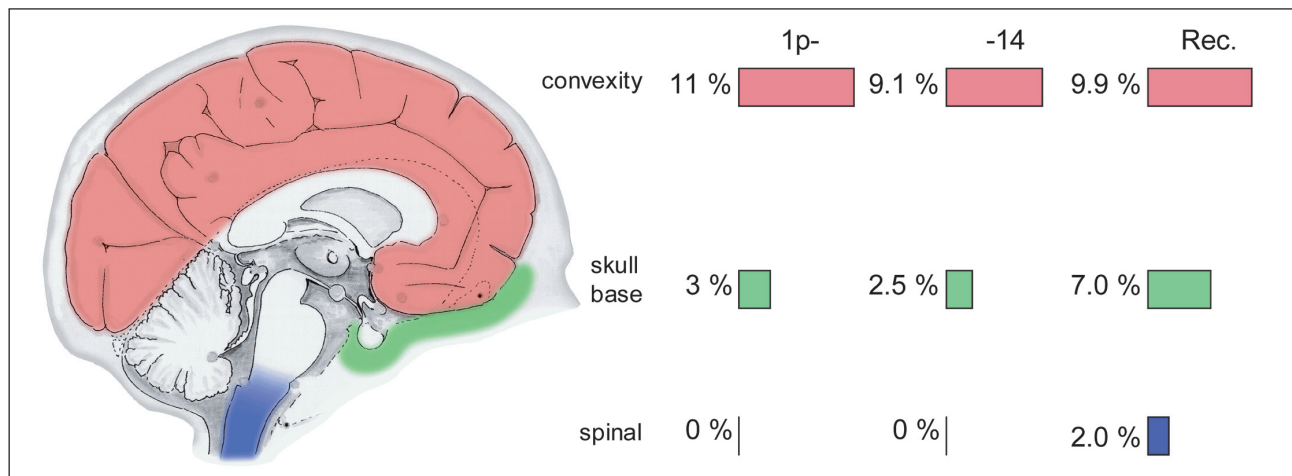


Figure 2. Bar plots for chromosomal aberrations (1p-, -14) and recurrence [Rec] according to brain regions. Red color indicates convexity, green color skull base, and blue color spinal tumours. Reprinted with permission from [Ketter R, Rahnenführer J, Henn W, Kim YJ, Feiden W, Steudel WI, Zang KD, Urbschat S. Correspondence of tumor localization with tumor recurrence and cytogenetic progression in meningiomas. *Neurosurgery* 2008; 62 (1): 61–9; discussion 69–70]. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

activity (MI) are defined for each grade by the WHO classification of brain tumours and because MI can be applied as the sole grading criterion, the reliable and reproducible assessment of MI is crucial for appropriate risk stratification. In 2007, we classified 661 meningiomas according to their genetic progression scores (GPS values) [18]. We found a high correlation between cytogenetic findings and histomorphology: higher genetic progression scores correlated highly significantly with higher histological grades ($p < 10^{-10}$, Fisher's exact test). This result is important since in the literature no clear correlation between histological grading and the rate of recurrence in meningiomas has been reported [9, 24, 25]. In our study, no clear distinction between the histological grades I and II with respect to tumour recurrence could be shown, either (Figure 1). However, WHO grade-III meningiomas show a statistically significant correlation with earlier tumour recurrence.

Expression of the Alkaline Phosphatase ALPL in Meningiomas

More than 4 decades ago, Osske and Jänisch [26] reported differences in the expression of ALPL in meningiomas. However, no clear correlation with tumour grade or subtype was found. It could be shown that there is a strong homogeneous expression of this enzyme in low-grade meningiomas, with increasing patchwork-like patterns of expression loss in anaplastic meningiomas [15]. ALPL is located on the short arm of chromosome 1 (1p34–1, p36.1). In a more detailed study using interphase FISH on frozen sections of native meningioma cells [3, 27], the authors were able to show a complete correlation between losses in 1p and reductions in the amount and activity of alkaline phosphatase (Figure 1). As the activity of alkaline phosphatase can easily be detected histochemically and is highly correlated with the presence of 1p, this prognostically relevant parameter is also available to non-cytogeneticists. The data speak in favour of a tumour suppressor gene function of ALPL; however, the mechanism of inactivation of the second allele is not yet explained.

Oncogenetic Tree Models

The basis for the oncogenetic tree mixture models are single oncogenetic trees as introduced by Desper et al [28] that can

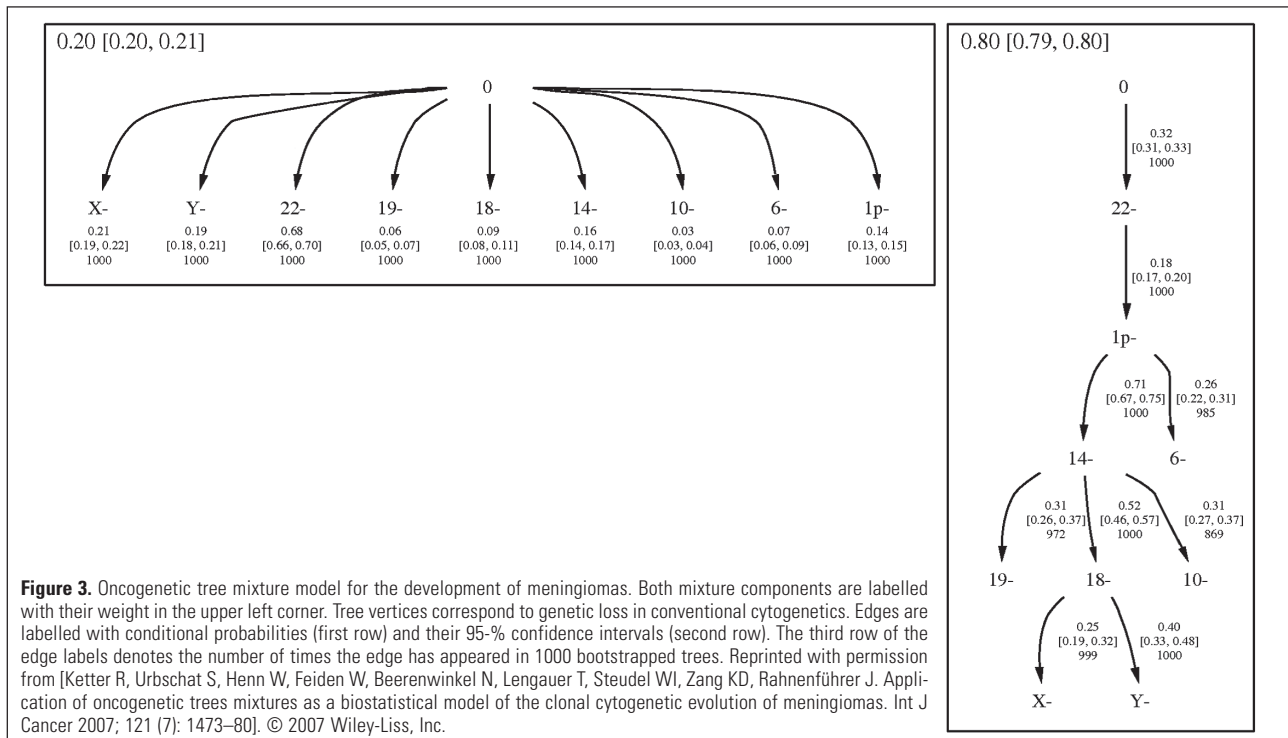
be used to estimate the most likely pathogenetic routes in tumours from observed subsets of genetic events. These models are of high explanatory power, but often only for a portion of the analyzed tumour samples. A subset of genetic events is only represented by this tree model if for any event in this subset all precursor events in the tree also belong to the subset. All other subsets of events are assigned likelihood zero. Von Heydebreck et al [29] propose to include additional hidden events in the tree and to model genetic events as leaves in the tree. This method trades feasibility of maximum-likelihood estimation of oncogenetic trees with reduced interpretability due to the introduction of hidden events.

We introduced mixture models of the single oncogenetic trees as used in Desper et al [28]. In these mixture models, one tree component is restricted to have a star-like topology, representing independence between genetic events. Owing to the starlike component, every combination of genetic events is represented in the model. The oncogenetic tree mixture models combine interpretability of the trees of Desper et al [28] with an appropriate probabilistic framework.

Relevance of Gender for Genetic Progression Models

Breaking down the oncogenetic tree by gender, there is a reversal concerning chromosomes 14 and 1p– in the male population. For males, monosomy 14 is estimated to be an earlier event followed by the deletion of the short arm of one chromosome 1. Monosomy 14 has been found to be associated with aggressive behaviour of meningiomas [14, 24, 25, 30, 31]. However, in the literature the loss of chromosome 14 has never been correlated with gender. It is well known that females predominate over males with a ratio of 2.67:1 when it comes to the overall incidence of meningiomas.

It could be shown that the deletion of the short arm of one chromosome 1 has to be regarded as a more valid cytogenetic parameter than monosomy 14 for the prediction of tumour recurrence, particularly because all anaplastic meningiomas in our series displayed a deletion of chromosome 1p (Figure 3).



Predictive Value of Genetic Progression Scores for Tumour Recurrence

We introduce the GPS of a tumour as the estimated average waiting time of its observed genetic pattern in the timed oncogenetic tree. Using Cox regression analysis, we demonstrate that for meningiomas the GPS has prognostic value with respect to clinical outcome and recurrence (Figure 4). Previously, it was shown that the information gain due to GPS holds true also for tumour samples from 2 other cancer types with notably different genetic backgrounds, namely glioblastoma and prostate cancer [19].

Strong correlations were found between histological measurements and the GPS. Interestingly, histological grades I and II alone were not informative with respect to recurrence of meningioma. Figure 4 shows the clinical relevance of the calculated GPS classification broken down to the WHO classification. This demonstrates that the genetic aberrations, especially the deletion of 1p, are independent markers for the clinical courses of meningiomas. Thus, the GPS classification allows a prognostically significant distinction between low-risk and high-risk meningiomas at the time of primary surgery. It can be expected that a combination of both histopathological and cytogenetical description of meningiomas could result in improved prognostic accuracy [3, 12, 32].

Accordingly, the deletion of the short arm of one chromosome 1 is an independent prognostic factor which correlates significantly with a raised risk of recurrence. Due to the limited follow-up period we have to expect that the recurrence rate may further increase over time.

Our results are in agreement with former cytogenetic investigations which indicated that the deletion of the distal part of the short arm of a chromosome 1 (1p-) is associated with pro-

gression in meningiomas [3, 10–14, 27, 33]. After initial speculation on the role of 1p deletion for tumour recurrence [10], the importance of this aberration beside monosomy 22, 14, and 10 for the development of atypical and anaplastic meningiomas [13] and for progression from typical to atypical meningioma [15] has been pointed out.

Further Parameters Involved in Meningioma Progression, Infiltration, and Recurrence

A very peculiar phenomenon in meningioma is invasion into the neighbouring anatomical structures, such as brain tissue and skull bone. Extracellular matrix (ECM) degradation by several proteolytic enzyme systems is a critical step in tumour infiltration. Matrix metalloproteases (MMP) are involved in the degradation of ECM components such as collagen and proteoglycans in normal embryogenesis and remodelling as well as in many disease processes such as tumour development, invasion, and progression. Okuducu et al [34] found an association between transcription factor Ets-1, the main regulator of several MMPs, and MMP-2 and -9 expression indicating a possible role for Ets-1 in MMP regulation in meningiomas. They found that increased Ets-1 expression was associated with high WHO grades in meningiomas, offering a possible additional diagnostic and prognostic tool for the evaluation of meningiomas [34].

The increasing frequency of chromosome aberrations in higher-grade meningiomas might be the result of loss of apoptotic control. Surprisingly, data on TP53 are relatively scarce and inconsistent. With common SSCP techniques, mutations have rarely been detected. However, histochemically there appears to be a significant accumulation of (inactive) p53 protein in higher-grade and recurrent meningiomas [35].

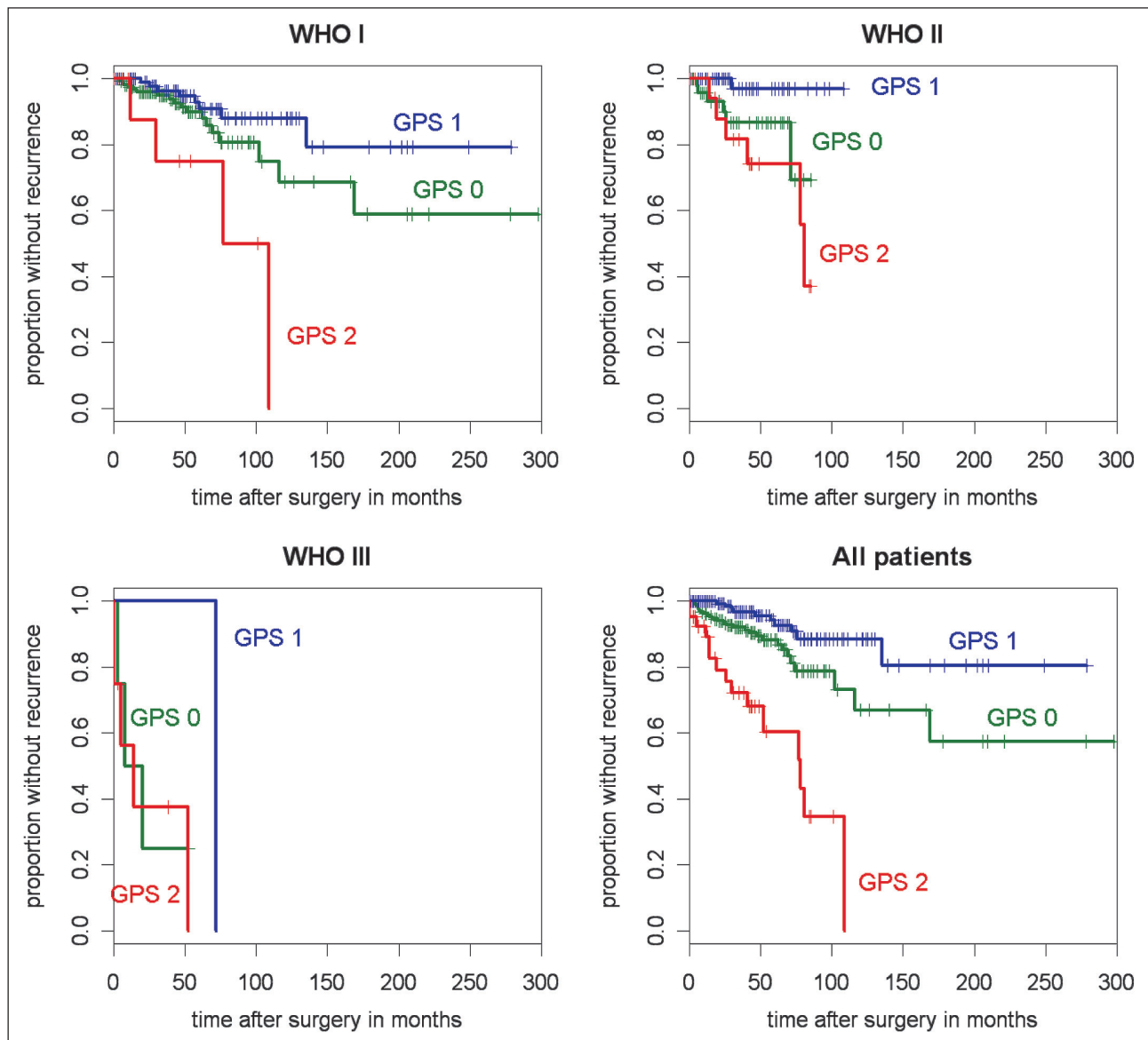


Figure 4. Kaplan-Meier survival curves for time to recurrence of meningioma patients; patients are split into 3 subgroups according to grouping based on the genetic progression score (green line: $\text{GPS} \leq 1.81$, blue line: $1.81 < \text{GPS} \leq 6.39$, red line: $6.39 < \text{GPS}$). In the first 3 plots, only subsets of patients according to WHO grade are considered. Reprinted with permission from [Ketter R, Urbschat S, Henn W, Feiden W, Beerenwinkel N, Lengauer T, Steudel WJ, Zang KD, Rahnenführer J. Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas. *Int J Cancer* 2007; 121 (7): 1473–80]. © 2007 Wiley-Liss, Inc.

A further gene located on chromosome 22 is the gene for the tissue inhibitor of metalloproteinase 3 (TIMP3) on 22q12.3. In 2010, Barski et al [36] examined a series of 50 meningiomas, including 27 benign meningiomas (World Health Organization [WHO] grade I), 11 atypical meningiomas (WHO grade II) and 12 anaplastic meningiomas (WHO grade III). They found hypermethylation of TIMP3 in 67 % of anaplastic meningiomas, but only 22 % of atypical and 17 % of benign meningiomas. Therefore, TIMP3 inactivation by methylation seems to be involved in meningioma progression as well, at least it is associated with a more aggressive, high-grade meningioma phenotype [36].

Especially the deletion of chromosome 1p was ascertained to be an early and crucial event in the progression in meningiomas. In order to verify the information gain due to GPS, it is of particular interest to demonstrate improved performance over established histopathological parameters. By fitting multi-

variate Cox regression models we also found that for meningiomas the GPS is prognostic also after adjustment for age. The GPS can thus be used to further identify subgroups. We define low-risk patients as those with histological WHO grade-I tumours that belong to GPS group 0 or 1, and high-risk patients as those who harbour tumours that are grade II or III and/or belong to GPS group 2. High-risk patients should undergo an intensified regimen of postoperative surveillance including NMR follow-up every 6 months and glucose PET studies to assess the biological activity of early recurrent tumour growth. Consequently, a multimodal approach to meningioma grading is most promising for identifying meningiomas with an increased tendency to recur and for planning their follow-ups.

Conflict of Interest

None.

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